West Coast Transplant ID Meeting 12/4/2024

Chelsea Morinishi, PGY-5
UCLA ID Multicampus Fellowship

Objectives

- Discuss the management approach to refractory and resistant CMV infection
- Analyze the utility of maribavir in this treatment cascade
- Consider clinical scenarios for the use of maribavir

Cytomegalovirus: Impact on the Transplanted Host

- CMV has multiple indirect effects which confer higher morbidity and mortality
  - Pro-inflammatory state ➞ association with vascular disease, chronic rejection
  - Reduced humoral and cellular immunity ➞ increased risk of bacterial and invasive fungal infection

- Antiviral prophylaxis and treatment pose various challenges (i.e. refractory and resistant infection)

Refractory and Resistant CMV Infection

- **Refractory CMV infection**: persistent or worsening symptoms or DNAemia despite appropriately dosed antiviral therapy for > 2 weeks
- **Resistant CMV infection:** above conditions AND detection of mutation conferring antiviral resistance
- Should also consider history of antiviral exposure

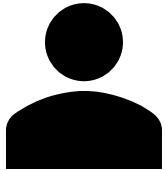
Ljungman et al. *Clin Infect Dis*. 2024;79(3):787-794.

Risk Factors for Refractory and Resistant CMV Infection

- Lymphocyte-depleting immunosuppression (e.g. anti-thymocyte globulin)
- High risk serostatus (D+/R- in SOT, R+ in HCT)
- Lung transplant recipients
- Prior prolonged exposure to antiviral therapy (>8 weeks)
- Suboptimal dosing of antiviral therapy

1) Fisher C.E. et al. Clin Infect Dis. 2017;65(1):57-63; 2) Acquier M et al. *Open Forum Infect Dis*. 2023;10(2):ofad018

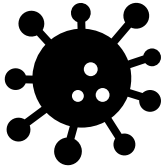
Case Presentation: Introduction



[redacted]-year-old [redacted] with a history of idiopathic pulmonary fibrosis and short telomere syndrome s/p bilateral orthotopic lung transplant

- Induction: basiliximab
- Maintenance: tacrolimus, MMF, prednisone 10 mg qd
- CMV Serostatus: CMV D-/R-

Case Presentation: Admission



- Admitted ~90+ days after BOLT for CMV PCR of 9,340, found on serial monitoring
- Asymptomatic

- Prior to admission, on day 30 post-BOLT: routine bronchoscopy/BAL were performed. BAL washings + CMV (CT 29), rare CMV positive cells on transbronchial bx. No clinical symptoms of pneumonitis.
- Treated with valganciclovir 900 mg PO BID until negative VL, then transitioned to secondary prophylaxis dosing.
- Prior CMV serostatus suspected false negative donor.

05/15/23	08:32	<137
05/08/23	08:23	<137
05/01/23	08:22	<137
04/24/23	08:38	<137
04/11/23	09:18	<137
04/03/23	08:52	202
03/21/23	09:49	3,287
03/16/23	08:32	1,830
03/13/23	08:25	1,018
03/06/23	08:33	996

Admission Labs

- WBC 2.01 cells/μL
- Platelet 96,000 cells/μL
- Creatinine 0.87, CrCl 59.4 mL/min
- Potassium 4.0
- Peak CMV viral load of 34,600 IU/mL (4 days before admission)

Poll #1: What would you do next?

a) Increase valganciclovir to treatment dose

b) Change to ganciclovir (renally dosed)

c) Change to foscarnet

d) Change to maribavir

e) Change to cidofovir

Poll #1: What would you do next?

a) Increase valganciclovir to treatment dose

b) Change to ganciclovir (renally dosed)

c) Change to foscarnet

d) Change to maribavir

e) Change to cidofovir

Clinical Course

- Started foscarnet 70 mg/kg q12 (renally dosed).
- Repeat CMV PCR 1 week later decreased to 4,930 IU/mL (1 log).
- Viracor CMV genotypic assay confirmed UL94 mutation (L595S), confirming GCV resistance.
- Patient developed severe nausea secondary to foscarnet.

Poll #2: What would your next step be?

a) Continue foscarnet at current dose

b) Switch to maribavir

c) Switch to intravenous ganciclovir

d) Switch to high dose letermovir

Poll #2: What would your next step be?

a) Continue foscarnet at current dose

b) Switch to maribavir

c) Switch to intravenous ganciclovir

d) Switch to high dose letermovir

Clinical Course (continued)

Foscarnet was discontinued. Initiated Maribavir 400 mg PO BID.

At time of switch to MBV, ANC was 0.92 x 10E3/uL and ALC was 0.649 x 10E3/uL, and CrCl 53.

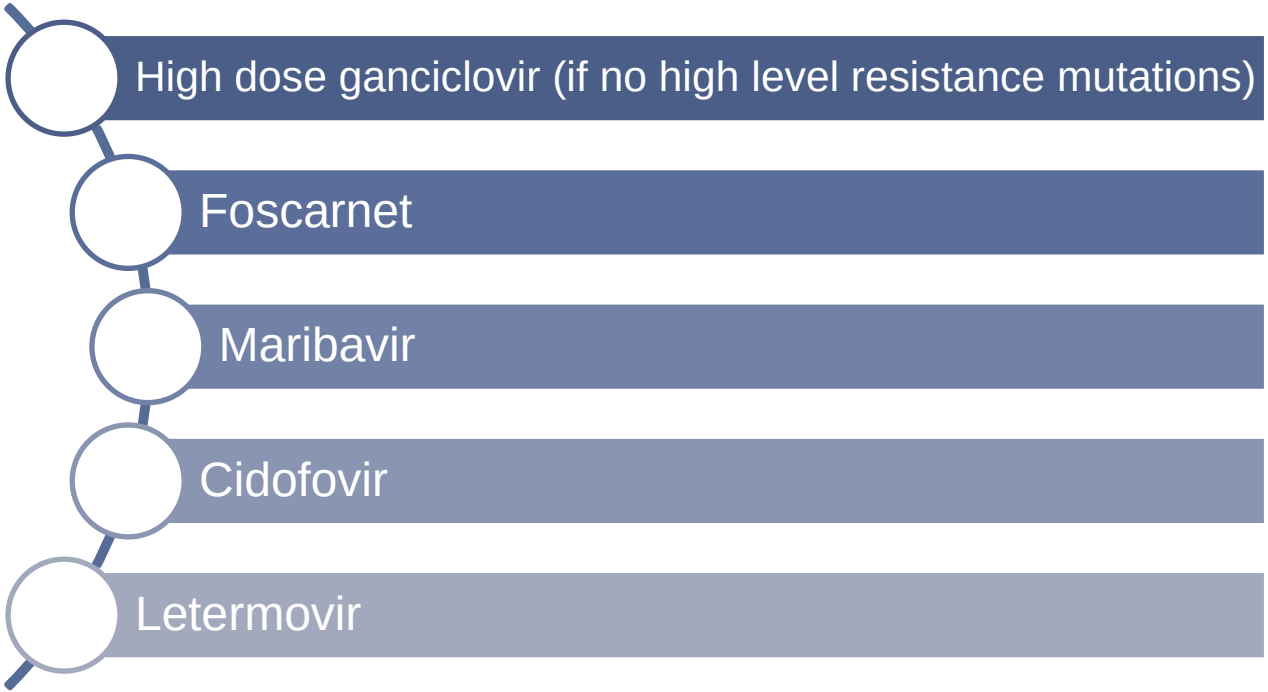
Achieved sustained clearance with VL <137 after 29 days of maribavir.

07/20/23	08:43	<137
07/14/23	09:11	315
07/10/23	10:05	168
07/03/23	08:54	3,430
06/29/23	08:28	5,980
06/26/23	09:11	7,200
06/23/23	11:53	9,340
06/19/23	17:07	4,920
06/12/23	10:42	34,600
06/06/23	09:08	13,100
05/30/23	09:45	5,787

Poll #3: What do you use for CMV genotype testing?

a) Eurofins Viracor
b) ARUP
c) Mayo Clinic
d) Other
e) Not sure

Treatment Options for R/R CMV Infection



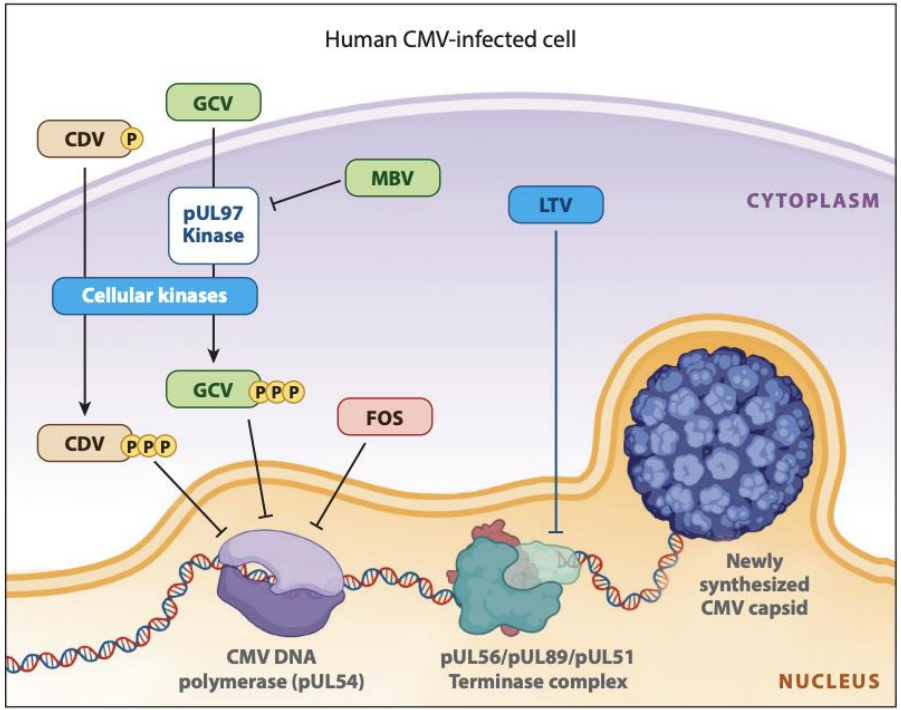
High dose ganciclovir (if no high level resistance mutations)	**Not an option given L595S mutation (in this case)**
Foscarnet	**Risk of GI upset, electrolyte imbalance, renal insufficiency, genital ulcers**
Maribavir	
Cidofovir	**Risk of renal insufficiency, myelosuppression, uveitis**
Letermovir	**Off-label use as treatment; suboptimal choice as monotherapy**

Advantages of Maribavir

- Oral formulation
- Well-tolerated without effects on bone marrow, renal function, or electrolytes
  - Most common side effect: dysgeusia
- No renal dose adjustment necessary
- Distinct mechanism of action

Differences in Antiviral Mechanism of Action

- Maribavir has a different mechanism of action from traditional antivirals:
  - inhibits CMV kinase, which phosphorylates key enzymes involved in DNA replication, encapsidation, nuclear egress of viral capsids
  - Antagonizes activity of ganciclovir and valganciclovir



Saullo and Miller. *Annual Review of Medicine*. 2023. 74:89–105

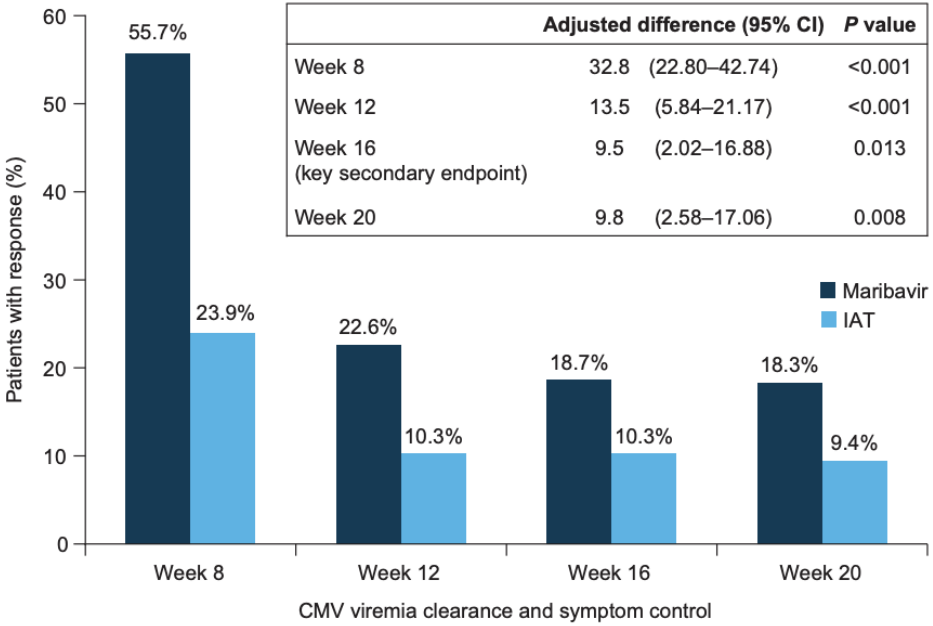
SOLSTICE Trial (2022): Phase 3 Trial on Maribavir for R/R CMV

- **Primary outcome:** clearance of CMV DNAemia and symptom control at week 8
- **Protocol:** Randomization to maribavir group vs. investigator-assigned therapy group (VGC/GCV, CDV, or FOS)
- **Sample size:** 352 adult patients (40.1% SOT and 59.9% HCT)
- **Key baseline characteristics:**
  - Majority of SOT was kidney > lung
  - ~60-72% patients had low baseline CMV level (<9100 IU/mL) vs. 6% with high level (>91,000 IU/mL)
  - ~50% had refractory and resistant CMV infection

Avery RK, et al. *Clin Infect Dis*. 2022;75:690-701.

SOLSTICE Trial (2022)

Maribavir was superior to investigator-assigned therapy in achieving viremia clearance and symptom control at primary (8 weeks) and secondary endpoints (16, 20 weeks)

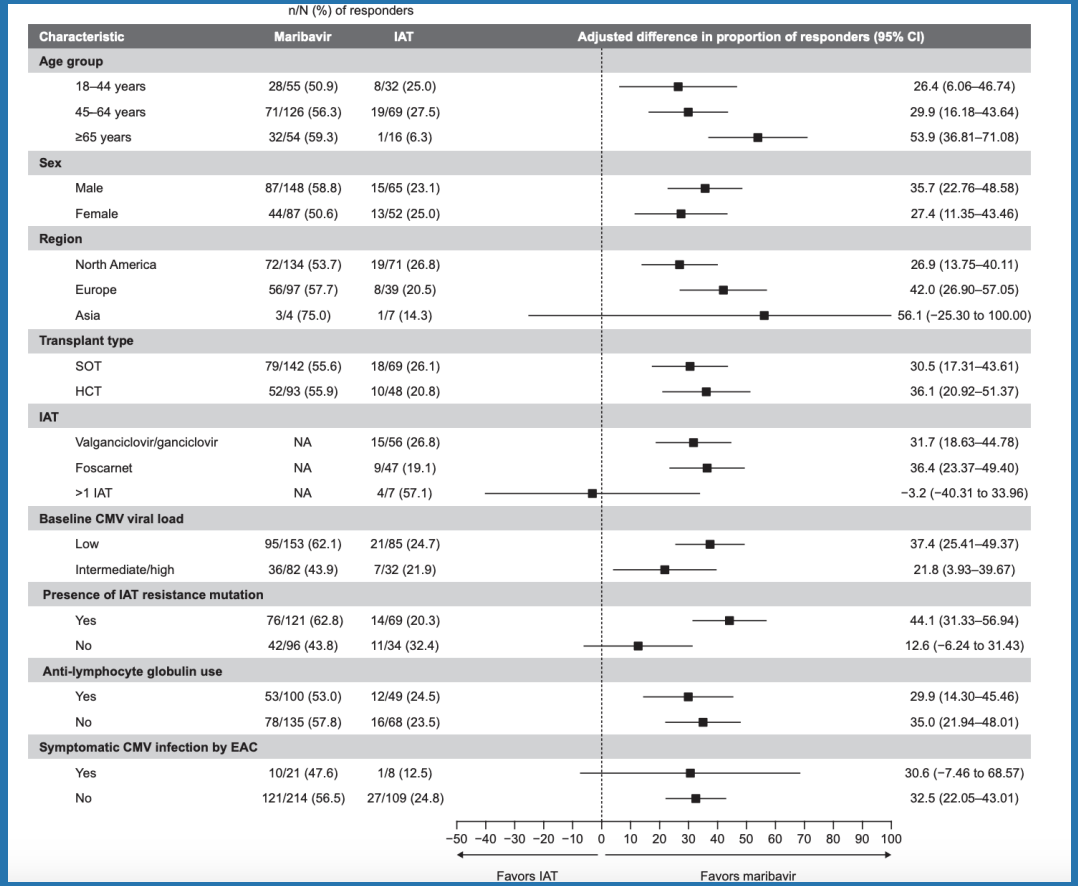


	Adjusted difference (95% CI)		*P* value
Week 8	32.8	(22.80–42.74)	<0.001
Week 12	13.5	(5.84–21.17)	<0.001
Week 16 (key secondary endpoint)	9.5	(2.02–16.88)	0.013
Week 20	9.8	(2.58–17.06)	0.008

Avery RK, et al. *Clin Infect Dis*. 2022;75:690-701.

SOLSTICE Trial (2022): Subgroup Analyses

- More favorable outcome for MBV with lower baseline CMV viral load
- No significant difference between IAT and MBV in symptomatic CMV infection



Avery RK, et al. *Clin Infect Dis*. 2022;75:690-701.

Poll #4: When do you most commonly use maribavir at your institution?

a) At initiation in patients with myelosuppression

b) At initiation in treatment-experienced patients with other risk factors for antiviral resistance

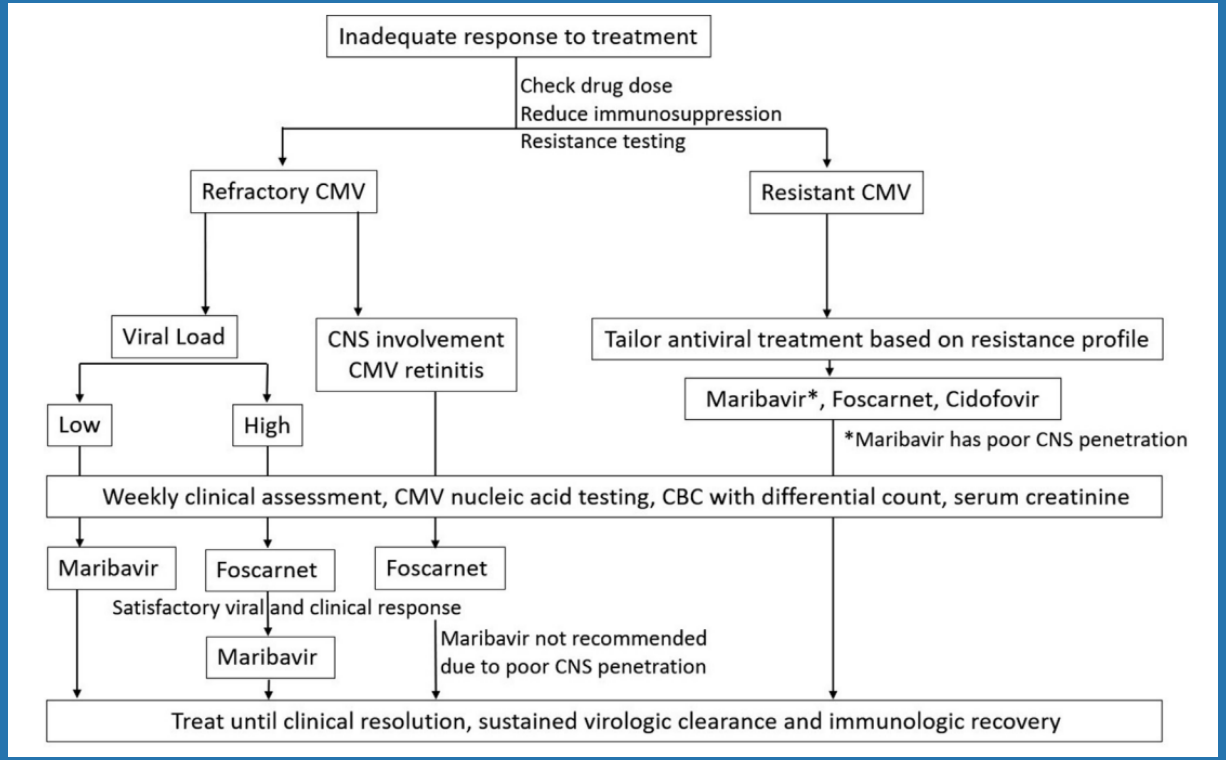
c) As above, but only with low level, asymptomatic CMV DNAemia

d) After successful treatment with foscarnet for consolidation therapy

e) At initiation in patients with ganciclovir resistance and tissue-invasive disease

f) Secondary prophylaxis in SOT or HSCT recipients

Proposed Algorithm for R/R CMV Treatment



Razonable R. *Clin Microbiol Infect*. 2023;29(9):1144-1149.

Ni et al. 2024: Real World Experience with MBV for Treatment of CMV in High-Risk Solid-Organ Transplant Recipients

- Single-center, retrospective study of maribavir treatment outcomes for R/R CMV in SOT recipients
- 13 patients, 15 treatment episodes
- 73% had asymptomatic CMV DNAemia, 27% with probably or proven CMV disease

40% of episodes resulted in viral clearance

33% of patients who achieved viral clearance developed recurrent CMV DNAemia within 4 weeks of MBV discontinuation

47% of treatment episodes resulted in either MBV resistance or recurrent DNAemia – higher viral loads seen

Ni B, et al. *Open Forum infect Dis*. 2024;11(7):ofae335.

Clinical Course (continued)

Within 2 weeks of clearance, developed viral load increased to 1100 while on MBV

ARUP CMV genotype assay confirmed new UL97 (H411Y, T409M) mutations, confirming MBV resistance

Switched to foscarnet

CMV INSIGHT T-cell immunity panel CD8 0.03 CD4 0.18%, indicating impaired CMV immunity

Cleared CMV DNAemia, but low level DNAemia up to 4.5K while off therapy. Foscarnet resumed. Clearance achieved. Transitioned to letermovir for prophylaxis.

10/22/23	15:56	160
10/19/23	15:27	92.7
10/15/23	06:08	47.4
10/08/23	06:08	322
10/02/23	08:28	4,510
09/25/23	08:19	359
09/21/23	10:42	<137
09/18/23	08:51	<137
09/10/23	16:29	<137
09/07/23	16:03	<137
08/31/23	17:16	1,390
08/27/23	06:51	1,000
08/20/23	06:19	1,100
08/13/23	11:28	849
08/10/23	09:20	1,110
08/03/23	09:04	<137

Key Takeaways

- There are several considerations in antiviral selection for refractory and resistant CMV infection:
  - Absorption
  - Tissue involvement/drug penetration
  - Baseline viral load
  - Renal insufficiency
  - Presence of resistance mutations or extensive history of antiviral exposure

Key Takeaways

- Compared with traditional antivirals, maribavir is well-tolerated and more effective than traditional antivirals in CMV clearance in low-moderate CMV DNAemia
- Maribavir can be useful as stepdown therapy after reduction in viral load
- Maribavir resistance has been described after successful treatment, with high CMV viral loads and lymphopenia as risk factors

References

Acquier M, Taton B, Alain S, et al. Cytomegalovirus DNAemia Requiring (Val)Ganciclovir Treatment for More Than 8 Weeks Is a Key Factor in the Development of Antiviral Drug Resistance. *Open Forum Infect Dis*. 2023;10(2):ofad018. Published 2023 Jan 23. doi:10.1093/ofid/ofad018

Avery RK, Alain S, Alexander BD, et al. Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial [published correction appears in Clin Infect Dis. 2023 Feb 8;76(3):560. doi: 10.1093/cid/ciac970]. *Clin Infect Dis*. 2022;75(4):690-701. doi:10.1093/cid/ciab988

Fisher CE, Knudsen JL, Lease ED, et al. Risk Factors and Outcomes of Ganciclovir-Resistant Cytomegalovirus Infection in Solid Organ Transplant Recipients. *Clin Infect Dis*. 2017;65(1):57-63. doi:10.1093/cid/cix259

Ljungman P, Chemaly RF, Khawaya F, et al. Consensus Definitions of Cytomegalovirus (CMV) Infection and Disease in Transplant Patients Including Resistant and Refractory CMV for Use in Clinical Trials: 2024 Update From the Transplant Associated Virus Infections Forum. *Clin Infect Dis*. 2024;79(3):787-794. doi:10.1093/cid/ciae321

Ni B, Wolfe CR, Arif S, et al. Real-World Experience With Maribavir for Treatment of Cytomegalovirus Infection in High-Risk Solid Organ Transplant Recipients. *Open Forum Infect Dis*. 2024;11(7):ofae335. Published 2024 Jun 15. doi:10.1093/ofid/ofae335

Razonable RR. Oral antiviral drugs for treatment of cytomegalovirus in transplant recipients. *Clin Microbiol Infect*. 2023;29(9):1144-1149. doi:10.1016/j.cmi.2023.03.020

Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13512. doi:10.1111/ctr.13512

Saullo JL, Miller RA. Cytomegalovirus Therapy: Role of Letermovir in Prophylaxis and Treatment in Transplant Recipients. *Annu Rev Med*. 2023;74:89-105. doi:10.1146/annurev-med-042921-124739